REVIEW ARTICLE

Diagnosis and Treatment of Patients with Thyroid Cancer

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BACKGROUND: Thyroid cancer is the most common malignancy of the endocrine system, representing 3.8% of all new cancer cases in the United States and is the ninth most common cancer overall. The American Cancer Society estimates that 62,450 people in the United States will be diagnosed with thyroid cancer in 2015, and 1950 deaths will result from the disease.

OBJECTIVE: To review the current approach to the diagnosis and treatment of patients with thyroid cancer.

DISCUSSION: Over the past 3 decades, there has been a dramatic increase in the number of people diagnosed with thyroid cancer, which may be attributable to the wide use of imaging studies, including ultrasounds, computed tomography, magnetic resonance imaging, and positron emission tomography scans that incidentally detect thyroid nodules. Thyroid cancer is divided into several main types, with papillary thyroid cancer being the most common. The treatment options for patients with thyroid cancer include the surgical removal of the entire thyroid gland (total thyroidectomy), radioactive iodine therapy, and molecular-targeted therapies with tyrosine kinase inhibitors. This article summarizes the diagnosis and treatment of thyroid cancer, with recommendations from the American Thyroid Association regarding thyroid nodules and differentiated thyroid cancer. Recently approved drugs and treatment trends are also explored.

CONCLUSION: The prognosis and treatment of thyroid cancer depend on the tumor type and its stage at the time of diagnosis. Many thyroid cancers remain stable, microscopic, and indolent. The increasing treatment options for patients with thyroid cancer, including therapies that were recently approved by the US Food and Drug Administration, have kept the mortality rate from this malignancy low, despite the increase in its incidence. Early diagnosis and appropriate treatment can improve prognosis and reduce mortality.

KEY WORDS: endocrine system, thyroid cancer, thyroidectomy, tyrosine kinase inhibitors, radioactive iodine, fine-needle aspiration biopsy

The thyroid is an important endocrine gland located at the base of the throat anterior to the trachea. It is composed of 2 wing-shaped lobes and an isthmus that connects them, which normally cannot be palpated through the skin on physical examination. The thyroid uses iodine to secrete hormones that control the heart rate, blood pressure, body temperature, and basal metabolic rate.

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In the past 3 decades, there has been a dramatic increase in the number of people diagnosed with thyroid cancer.[1] According to the National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results Program, more than 500,000 people were living with thyroid cancer in the United States in 2011.[2] The American Cancer Society has projected more than 62,000 new cases of thyroid cancer and more than 1900 associated deaths in the United States for 2015.[3] Based on reports from the NCI, the incidence of thyroid cancer has risen over the past 10 years by an average of 5.5% annually, and the death rate rose by 0.8% annually from 2002 to 2011.[2]

Most recently, the number of new cases of thyroid cancer is estimated to be 12.9 per 100,000 men and women annually, and the number of associated deaths is estimated to be 0.5 per 100,000 men and women annually.[2] Still, the lifetime risk for thyroid cancer is approximately 1.1%, and the 5-year survival rate has risen to 97.8%, because almost 70% of cases are now

diagnosed at an early stage, when the cancer is localized at the gland.[2]

The rise in the incidence of thyroid cancers may be attributable to the widespread use of imaging studies, such as ultrasounds, computed tomography, magnetic resonance imaging, and positron emission tomography (PET) scans, that incidentally detect thyroid nodules.[4] This article is focused on the diagnostic and treatment approaches used for thyroid nodules and differentiated thyroid cancer (papillary and follicular cancer), which comprise almost 90% of all thyroid cancers, and the increased incidence has been almost entirely attributed to an increase in papillary thyroid cancer.[5]

Thyroid Nodules

Thyroid nodules are very common in the general population, and a great majority of them are benign.[4] A thyroid nodule is a growth of cells (a lump) in the thyroid gland, which is located in the anterior neck region. Radiologically, they are lesions within the thyroid gland that are distinct from the surrounding thyroid parenchyma. It is estimated that 3% to 7% of the world's population have a palpable nodule, and the prevalence may increase to more than 70% if patients are screened by ultrasound.[6] Regardless of palpability, approximately 5% of detected thyroid nodules are malignant, with the exception of nodules discovered by PET scans, which have a 33% increased risk for malignancy.[5,7] Thus, newly discovered thyroid nodules are clinically important, because of the need to exclude thyroid cancer.

Usually, only nodules measuring >1 cm are evaluated, unless there are other risk factors that increase the suspicion for malignancy. Pertinent risk factors include a history of radiation to the head and neck region, a family history of thyroid cancer or thyroid disease, suspicious ultrasound findings, lymphadenopathy, a history of goiter, female sex, and Asian ancestry.[1,5]

Thyroid cancer occurs more frequently in women than in men, at an approximate ratio of 3:1, and is more prevalent in the white and Asian/Pacific Islander populations than in other populations.[2,8] Thyroid cancer can occur in any age-group but more so in adults aged 45 to 54 years, with a mean age of 50 years at diagnosis.[2]

Along with a thyroid nodule, the symptoms of thyroid cancer include a painless swelling in the front of the neck, difficulty swallowing, difficulty breathing, hoarseness, or a change in voice, among others.[9]

Diagnostic Workup

The initial workup for any newly discovered thyroid nodule should include a serum thyroid-stimulating hormone (TSH) level.[5] The TSH is released from the anterior pituitary and signals the thyroid gland to make thyroid hormone as appropriate. When thyroid hormone levels are low, the TSH rises responsively and vice versa; thus, measuring a TSH level allows differentiation between functional and nonfunctional nodules. This is an important characteristic, because hyperfunctioning nodules are rarely malignant. However, if a TSH is subnormal, indicating a hyperactive gland, a nuclear medicine imaging study (thyroid uptake and scan) should be performed, to document whether the nodule itself is hyperfunctioning (hot), isofunctioning (warm), or nonfunctioning (cold) compared with the surrounding thyroid tissue. If the nodule is hot or warm, no cytologic evaluation is necessary; however, if the patient is symptomatic, additional evaluation is required to rule out other causes, such as Graves' disease, and to provide adequate treatment.

Nonfunctioning nodules will require the use of fine-needle aspiration (FNA) for cytologic evaluation. However, if the TSH is normal or elevated, even within the upper limits of normal, a FNA is recommended, because the rate of malignancy is higher with nonfunctioning nodules and glands affected by Hashimoto's thyroiditis, a common autoimmune hypothyroid disease.[5]

Along with serum TSH, a diagnostic neck ultrasound should be performed on all suspected nodules to confirm the existence of a nodule and to check for any suspicious features.[5] However, no single ultrasound feature and no combination of ultrasound features is sensitive enough or specific enough to identify malignancy by themselves. Some ultrasound features have greater correlation with

KEY POINTS

- The incidence of thyroid cancer, the most common endocrine system malignancy, is on the rise, likely because of widespread use of imaging studies
- The most common thyroid malignancy (70%-80%) and the least aggressive is papillary thyroid carcinoma
- The 5-year survival rate for thyroid cancer is 97.8%, thanks to early diagnosis and improved treatments
- Treatments vary by the cancer's stage and type, and include surgery (thyroidectomy), radioactive iodine, tyrosine kinase inhibitors (TKIs), and external beam radiation
- Surgery is the first-line therapy for differentiated tumors; total thyroidectomy has been demonstrated to increase survival and to decrease recurrence
- For advanced metastatic thyroid cancer, molecular-targeted therapies, including sorafenib, vandetanib, and cabozantinib, control thyroid progression and prolong progression-free survival

certain types of cancer, such as microcalcifications with papillary thyroid cancer and its absence in follicular thyroid cancer. Furthermore, certain sonographic features are highly predictive of benign nodules, such as purely cystic nodules and nodules with >50% spongiform appearance (aggregation of multiple microcystic components).[5] Of note, routine measurements of serum thyroglobulin and calcitonin for the initial diagnosis of thyroid cancer are not recommended.[5]

Fine-Needle Aspiration Biopsy

If the initial workup suggests a nonfunctional nodule with suspicious sonographic features, a FNA biopsy should be performed, because it remains the most accurate, cost-effective, and best diagnostic method for evaluating nodules.[5,10] FNA can be performed either with palpation or ultrasound guidance; however, ultrasound-guided FNA is preferred, especially when the nodules have cystic components, are located posteriorly, or are difficult to palpate. Ultrasound-guided FNA also reduces the need for repeat FNA biopsy secondary to inadequate samples.[5,10] The goal of the FNA biopsy is to obtain at least 6 follicular cell groups, each containing 10 to 15 cells from at least 2 different aspirates of a nodule for cytologic evaluation.[5]

In general, routine FNA is not recommended for subcentimeter nodules, unless their sonographic appearance is suspicious, as described earlier. In that case, further assessment of the lateral and central neck lymph nodes by ultrasound would be required.[5] If abnormal lymph nodes are detected, a FNA biopsy should be performed on the lymph node in addition to the thyroid nodule. A second exception to not performing a biopsy on a subcentimeter nodule is a patient with a history of high risk for malignancy, which includes irradiation exposure, a family history of thyroid cancer, a previous hemithyroidectomy for thyroid cancer, or having positive nodules as determined by a PET scan.[5]

When performing a FNA biopsy, some anatomic features may need to be considered for obtaining the best sample. Mixed cystic-solid nodules should be biopsied within the solid component, and cyst drainage may be performed if patients are symptomatic.[5] In the case of a multinodular gland that consists of 2 or more nodules measuring >1 cm, the nodule with suspicious sonographic features should be biopsied preferentially.[5] However, if none of the nodules is suspicious, only the largest nodule should be aspirated, and the rest should be observed with serial ultrasound examination.[5] If nuclear imaging was performed as a result of a low serum TSH, a FNA should be performed on the hypofunctioning nodules, with preference for those with suspicious sonographic features. Therefore, a general rule is to choose the nodule that is the least functional, and with the most suspicious features, or the largest if they look benign.[5]

FNA biopsy results are categorized as nondiagnostic, malignant, suspicious for malignancy (50%-75% risk), indeterminate or suspicious for neoplasm (20%-30% risk), follicular lesion of undetermined significance (5%-10% risk), and benign.[5] Nondiagnostic cytology occurs in samples that fail to meet cytologic adequacy, which requires at least 6 follicular-cell groups, each containing 10 to 15 cells from at least 2 different aspirates of a nodule. In such a case, a repeat ultrasound-guided FNA should follow.[5] However, 7% of nodules can continue to yield nondiagnostic cytology results that may be malignant, so these nodules should be closely monitored by serial ultrasound or surgery.[5]

Surgery should be more strongly considered with solid nodules. Indeterminate cytology (suspicious for follicular or Hürthle-cell neoplasm, or follicular lesion of undetermined significance) has an increased risk for malignancy, ranging from 15% to 30%; so, the use of molecular markers can be considered to guide management.[5] The American Thyroid Association also recommends thyroid lobectomy for patients with an indeterminate solitary nodule, and total thyroidectomy for large tumors >4 cm and patients who have a high-risk history for malignancy.[5] All cytology suggesting malignancy requires surgery with either lobectomy or total thyroidectomy, unless there are contraindications or diffuse metastasis.

Finally, if a nodule is benign on cytology, no further immediate workup or treatment is required. Serial ultrasound examinations should be performed every 6 to 18 months to monitor for growth. If there is a more than 50% change in volume or a more than 20% increase in at least 2 dimensions, with a minimal increase of 2 mm in solid nodules, a FNA biopsy should then be repeated.[5]

Thyroid Cancer and Staging

Thyroid cancer is diagnosed histologically via FNA biopsy and is categorized into 4 main types. Representing approximately 70% to 80% of thyroid cancers, papillary thyroid carcinoma is the most common thyroid malignancy.[5,8] Papillary thyroid carcinoma is the least aggressive type of cancer, because it tends to grow and metastasize slowly.[5,8] It is composed of multifocal papillary and follicular elements forming sites of adenocarcinomas.[8]

Follicular thyroid carcinoma accounts for approximately 14% of thyroid cancers, is more aggressive than papillary thyroid carcinoma, and may be associated with iodine deficiency.[5] Hürthle-cell carcinoma is a variant of follicular carcinoma that is treated the same way as follicular carcinoma.

Medullary thyroid carcinoma, a cancer of nonthyroid cells that are normally present in the thyroid

gland, represents approximately 3% of thyroid cancers and is often associated with multiple endocrine neoplasia 2. Medullary carcinoma produces excess calcitonin, which makes it a useful tumor marker.[5,8]

Anaplastic thyroid carcinoma represents approximately 2% of thyroid cancers and is the most dangerous form of thyroid cancer, because it metastasizes early to the surrounding lymph nodes and distant sites.[11] Other thyroid malignancies, such as lymphoma and variants of the 4 types mentioned above, make up the remaining thyroid cancers. Clinically, thyroid cancer has been divided into 2 categories: (1) well-differentiated, including papillary and follicular cancers, and (2) poorly differentiated, including medullary and anaplastic cancers.

After a diagnosis of thyroid cancer, it is important to perform preoperative staging and imaging, because it can alter the patient's prognosis and treatment course. Up to 50% of patients with differentiated thyroid cancer will have cervical lymph node involvement, despite the primary tumor size.[5] Thus, a preoperative neck ultrasound for contralateral lobe and cervical lymph nodes is recommended for all patients undergoing thyroidectomy for malignancy, to help identify possible metastasis; however, neck ultrasounds only identify 50% of the lymph nodes that are found during surgery.[5]

Lymph node metastasis can be confirmed by ultrasound-guided FNA on abnormal lymph nodes and/or the measurement of thyroglobulin in the needle washout if it would change the disease management.[5] These results are then used to stage the extent of the cancer.

The American Joint Committee on Cancer (AJCC) has designated thyroid cancer staging by the Tumor, Node, Metastasis (TNM) classification system.[8] The AJCC's TNM classification system is available online (at the AJCC website).[8]

In addition, thyroid cancer can be stages, using stages I to IV, with the TNM classification system based on the tumor type of thyroid cancer (**Table 1**).[8]

Treatment Options

Treatment options for thyroid cancer include surgery, radioactive iodine (^{131}I) therapy, and molecular-targeted therapies with several tyrosine kinase inhibitors (TKIs). The standard treatment options vary depending on the type and stage of the cancer. Different guidelines are available from various oncology organizations regarding the treatment options for thyroid cancer. **Table 2** (page 34) lists standard treatment options as recommended by the NCI.[8] Recommendations from the National Comprehensive Cancer Network are divided by cancer type and are available at www.nccn.org/patients/guidelines/cancers.aspx.

Table 1 TNM Stages of Thyroid Cancer by Tumor Type

Papillary and follicular cancer in patients aged <45 years
Stage I: papillary carcinoma is localized to the thyroid gland
Stage II: papillary carcinoma that has spread distantly
Papillary and follicular cancer in patients aged ≥45 years
Stage I: papillary carcinoma is localized to the thyroid gland
Stage II: tumor that is >2 cm but ≤4 cm and is limited to the thyroid gland
Stage III: tumor that is >4 cm and is limited to the thyroid or with minimal extrathyroid extension or positive lymph nodes limited to the pretracheal, paratracheal, or prelaryngeal/Delphian nodes
Stage IV: extension beyond the thyroid capsule to the soft tissues of the neck, cervical lymph node metastases, or distant metastases; the lungs and bone are the most frequent sites of spread
Medullary thyroid cancer
Stage 0: clinically occult disease detected by provocative biochemical screening
Stage I: tumor <2 cm
Stage II: tumor >2 cm but ≤4 cm with no metastases or >4 cm with minimal extrathyroid extension
Stage III: tumor of any size with metastases limited to the pretracheal, paratracheal, or prelaryngeal/Delphian lymph nodes
Stage IVA: moderately advanced with or without lymph node metastases [for T4a], but without distant metastases
Stage IVB: very advanced with or without lymph node metastases, but no distant metastases
Stage IVC: distant metastases
Anaplastic thyroid cancer
All patients are considered to have stage IV disease

TNM indicates Tumor, Node, Metastasis.
Source: National Cancer Institute. Thyroid cancer treatment (PDQ): stage information for thyroid cancer. www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional/page3.

Surgery

Surgical options for primary tumors include hemithyroidectomy, with or without isthmusectomy; near-total thyroidectomy (leaving <1 g of thyroid tissue adjacent to the recurrent laryngeal nerve); and total thyroidectomy (removing all visible thyroid tissue).[5] Overall, near-total or total thyroidectomy is recommended for the management of thyroid cancer in which the primary tumor measures ≥1.0 cm to 2.0 cm.[12] Subtotal lobectomy and unilateral lobectomy used to be performed in the past, but they are now deemed inappropriate for the treatment of patients with thyroid cancer; instead, extracapsular dissection is now recommended.[12,13]

Because of the high percentage (42.7%) of the multifocal distribution of thyroid cancer, removing the thyroid gland in its entirety reduces the chance for malignancy in the residual parenchyma.[14] It also allows for the correct risk assessment of the tumor, which is based on size and extracapsular infiltration.[14]

Thyroidectomy is also recommended because 5% to 10% of thyroid cancer recurrences are found in the contralateral lobe.[12] The new technologic improvements in devices used for total thyroidectomy, such as the hemostatic vessel-sealing device and nerve monitoring, have increased the safety of the procedure and the efficacy of removing the tissues in patients with malignancy.[15] Studies also show the cost-effectiveness of an initial total thyroidectomy for nodules that are suspicious for cancer based on a FNA biopsy versus initial lobectomy and intraoperative frozen section procedure.[6,16]

Because lymph node metastasis can be present in 20% to 90% of patients with papillary cancer, a therapeutic central compartment neck dissection should be performed along with the total thyroidectomy when lymph nodes are clinically involved.[5] Prophylactic central compartment neck dissection is also recommended for T3 or T4 tumors, despite no clinically involved lymph nodes.[5] No prophylactic dissection is recommended for smaller T1 or T2 noninvasive tumors.[5]

Table 2 NCI Treatment Recommendations for Thyroid Cancer

Stage I and II papillary and follicular thyroid cancer
• Total thyroidectomy (tumor ≥1 cm)
• Lobectomy (tumor <1 cm)
Stage III papillary and follicular thyroid cancer
• Total thyroidectomy plus removal of involved lymph nodes or other sites of extrathyroid disease
• ^{131}I ablation after total thyroidectomy if the tumor demonstrates uptake of this isotope
• External beam radiation therapy if ^{131}I uptake is minimal
Stage IV papillary and follicular thyroid cancer
• ^{131}I: metastases that demonstrate uptake of this isotope may be ablated by therapeutic doses of ^{131}I
• External beam radiation therapy for patients with localized lesions that are unresponsive to ^{131}I
• Resection of limited metastases, especially symptomatic metastases, should be considered when the tumor has no uptake of ^{131}I
• Thyroid-stimulating hormone suppression with thyroxine is also effective in many lesions that are not sensitive to ^{131}I
Medullary thyroid cancer
• Localized: total thyroidectomy followed by external beam radiation therapy for recurrent tumors
• Metastatic: palliative chemotherapy
Anaplastic thyroid cancer
• Surgery: tracheostomy if necessary; if confined to local area, total thyroidectomy
• External beam radiation therapy if tumor cannot be surgically excised
• Chemotherapy: doxorubicin plus cisplatin as radiation sensitizer; not responsive to ^{131}I therapy

NCI indicates National Cancer Institute.
Source: National Cancer Institute. Thyroid cancer treatment (PDQ). www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional.

Today, thyroidectomy is mostly performed as an outpatient surgery.[17] With proper education and counseling, patients are more apt to choose outpatient surgery; however, for the safety of the patient, contraindications need to be considered. The contraindications for outpatient thyroidectomy include noncompensated cardiac and/or respiratory disease, dialysis-dependent renal failure, anticoagulant therapy, seizure disorder, obstructive sleep apnea, mental impairment, pregnancy, unilateral vocal fold paralysis, thyrotoxicosis, and morbid obesity.[18] Other factors, such as support from family or friends and emotional stability, are important to the outcome of the outpatient surgery.

An analysis of 5121 patients undergoing outpatient thyroidectomy suggested that the morbidity and readmission rates are very low, with 0.92% of patients having perioperative morbidities and 2.17% of patients being readmitted within 30 days of the operation.[17] Nevertheless, as with any procedure, complications can arise. The 2 most common early postoperative complications of thyroidectomy are hypocalcemia (20%-30%) and recurrent laryngeal nerve injury (5%-11%).[19]

The risk for postoperative hypocalcemia is increased by several factors, including the venous drainage of the upper parathyroid glands, the location of the parathyroid glands and difficulty in identifying them, the presence of large goiters, Graves' disease, thyroid cancer that requires an extensive dissection of lymph nodes, and repeat exploration of the cervical region resulting in adhesions, as well as young age and female sex.[19] The risk for injury to the recurrent laryngeal nerve is low, with a rare complication of bilateral recurrent laryngeal nerve palsy. The risk for injury to the nerve is increased by reoperation, the underlying thyroid pathology, the invasion of adjacent structures, and the extent of the resection.[19] Another complication is postoperative hemorrhage, the incidence of which rises with increases in the weight and size of the thyroid gland.[19]

Unilateral lobectomy involves a smaller operative field than total thyroidectomy. Hematomas occur in approximately 1% of patients, with events occurring within the first 6 hours after surgery.[19] The early signs of hematoma include pronounced anterior swelling, sensation of tightness, and purple discoloration of the skin. The late signs of hematoma may include respiratory stridor and distress. With early care and patient education about the signs of hematomas, same-day hospital discharge has been shown to be safe.[18,19]

Although such complications are not completely avoidable, they can be reduced. The incidence of postoperative hypocalcemia can be reduced by starting the patient with oral supplementation of calcium plus vitamin D

1 week before surgery, and continued for 2 weeks after surgery.[19] The calcium and parathyroid hormone levels are obtained between 6 and 24 hours postoperatively.[20] In patients with low parathyroid hormone levels, oral calcitriol is also added to increase the absorption of calcium.[19]

The prevention of recurrent laryngeal nerve injury is dependent on preoperative and intraoperative measures. Preoperatively, patients should be examined for any preexisting laryngeal dysfunctions. Intraoperatively, careful dissection of the nerve, nerve monitoring, and the choice of hemostatic techniques are important.[19] Although there is a lack of definitive evidence regarding nerve preservation from nerve monitoring, its use is increasing because it can confirm the functional integrity of the nerve at the end of the thyroidectomy.[19] Hemostatic techniques that reduce the operative time as well as intraoperative bleeding include new energy devices, such as ultrasonic dissection and electrothermal bipolar vessel sealing systems.

In a study that included 217 patients who had a total thyroidectomy, the treatment of differentiated thyroid cancer with total thyroidectomy alone without ^{131}I ablation showed a low risk (2.3%) for disease recurrence.[21] In another study that included 43,227 patients who underwent total thyroidectomy and 8946 patients who underwent lobectomy, for tumors ≥1 cm, the risks for recurrence and death were 15% and 31% higher, respectively, in the lobectomy group (P = .04) than in the total thyroidectomy cohort (P = .009).[22]

Radioactive Iodine Ablation and Treatment

^{131}I has had an important role in the treatment and management of thyroid cancer since 1946.[23] It is used in coordination with thyroidectomy to completely ablate the thyroid gland and to postoperatively eradicate possible residual cancer.[23-25] ^{131}I works by entering the thyroid cells via the sodium iodide transporters and emitting short-wavelength beta rays, causing acute cell death. When administered the first time after surgery, it is referred to as ablation, whereas subsequent administrations for residual disease are referred to as treatment.[23,26]

Removing the remnant tissue serves to decrease the potential for relapse and also to increase the sensitivity of follow-up diagnostic tests (eg, whole-body scintigraphy scans and serum thyroglobulin levels) that facilitate the detection of metastatic or residual disease.[23] It is particularly useful for differentiated thyroid cancer, because they account for the majority of thyroid cancers and are associated with a 10-year survival rate of between 90% and 95%. This survival rate suggests a need for long-term surveillance and testing for recurrence.[24,27] Although it has mainly been used as an adjuvant therapy, ^{131}I therapy also remains the mainstay treatment for nonsurgical and incompletely resectable thyroid tumors, such as microscopic or metastatic disease.[26]

Several factors should be considered when starting a patient with ^{131}I therapy. The first factor to consider is operability, because surgery is the first-line treatment for differentiated cancers.[26,28] In addition, it is important to assess the iodine avidity of the affected tissues, because ^{131}I has to be transported into the tissue to have an effect. PET and posttherapy whole-body scans have been used for confirmation.

The disease site and tumor characteristics are important factors to note, because they affect the results of ^{131}I therapy, as is seen by the higher rates of cure with lung and soft-tissue metastases and with well-differentiated tumor histotypes as opposed to brain metastases and poorly differentiated tumors.[26,28]

In general, guidelines from the American Thyroid Association recommend ^{131}I ablation for known metastases, extrathyroidal extension, and tumor size >4 cm; or smaller tumors with high-risk features, such as vascular invasion and aggressive histologies.[28] On the other hand, the guidelines do not recommend ablation for unifocal or multifocal tumors <1 cm without high-risk features.[26,28]

The patient's general health status and treatment tolerability are important considerations as well, because side effects are common with ^{131}I therapy and include salivary gland dysfunction (>40%), abnormally dry eyes (25%), transient fertility reduction (20%), transient leukopenia, and thrombocytopenia.[29]

Finally, and most important, it is pertinent to confirm the absolute contraindications of pregnancy and breastfeeding with ^{131}I, because such treatment can interfere with a fetus's thyroid gland and cause a severe physical and mental underdevelopment condition known as cretinism.[28] Some relative contraindications include bone marrow depression, pulmonary function restriction, salivary gland function restriction, and neurologic symptoms that can be exacerbated with the accumulation of ^{131}I.[26,28]

In preparation for ^{131}I therapy, patients are initially placed on a low-iodine diet for 4 to 6 weeks before treatment or have 2 weeks of daily intake of <50 µg iodine to avoid competition between ^{131}I and normal iodine.[28] Similarly, patients who have high iatrogenic loads of iodine (eg, amiodarone or contrast) cannot receive treatment until their urine iodine level falls to 100 µg per 24 hours.[28] Then, patients are placed on a regimen that can sufficiently elevate the serum TSH level to ≥30 mU/L to increase the number of sodium iodide symporters and to optimize the uptake of ^{131}I.[26]

This is achieved via thyroid hormone withdrawal or the use of the newer recombinant human thyroid stimulating hormone (rhTSH).[26] rhTSH was initially intro-

duced in 1998 for diagnostic purposes[30] and was approved for use before treatment with ^{131}I in 2007 by the US Food and Drug Administration (FDA).

The main concern with thyroid hormone withdrawal is possible iatrogenic hypothyroidism, which may last several weeks; however, the concern with rhTSH is its efficacy. Recent studies have shown that rhTSH is as effective as thyroid hormone withdrawal with ^{131}I thyroid remnant ablation, with significant benefits to the patient on health-related quality of life, adverse effects during and after ablation, and decreased whole-body radiation exposure.[31-33]

Once the appropriate TSH level is reached, ^{131}I is administered orally as a capsule at the proper amount of activity. After a single dose of ^{131}I, several tests are performed to verify successful treatment. The ^{131}I uptake is usually confirmed 2 to 8 days after treatment with a whole-body scan, and a follow-up scan is normally performed 6 to 12 months later.[28] The stimulated thyroglobulin levels (thyroglobulin levels drawn when TSH is high) and thyroid ultrasounds should also be checked at that time to monitor response; however, "lower risk patients with negative thyroglobulin levels may not require follow-up scanning at all."[28] A successful treatment is confirmed if there is <0.1% ^{131}I uptake within the thyroid bed on the follow-up scan and a low stimulated thyroglobulin level. A neck ultrasound should reveal an empty thyroid bed, with no new growths or extensions.[28]

Tyrosine Kinase Inhibitors

Radioactive iodine therapy is the staple treatment for recurrent or metastatic thyroid cancers; however, in patients whose cancer no longer takes up iodine, another treatment option is needed.

Many genetic alterations have been identified involving tyrosine kinase signaling pathways, including the *RET*, *RAF*, or *RAS* protein kinase genes, which lead to the activation of the tyrosine kinase domain.[34] The *RET/RAS/RAF* pathway is interconnected with the epidermal growth factor receptor–activated cascade, which leads to the syntheses of vascular endothelial growth factor (VEGF) and VEGF receptor.[34] Gain-of-function mutations in the *BRAF* oncogene, which confer new or enhanced activity on a protein, are the most frequent genetic alterations found in patients with papillary thyroid cancer, occurring in approximately 45% to 70% of these tumors in adults.[35-37] The overexpression of VEGF and other growth factors is frequently found in tumors that originated in the thyroid, particularly in tumors with *BRAF* mutations.[38] Drugs targeting these pathways could play a significant role in controlling the progression of the disease.

Vandetanib. In 2011, the FDA approved vandetanib, which targets *RET*, *EGFR*, and VEGF receptor for the treatment of patients with symptomatic or progressive, unresectable, locally advanced or metastatic medullary thyroid cancer. The approval of the first drug for this indication was based on data from the phase 3 Zactima Efficacy in Thyroid Cancer Assessment (ZETA) study.[39] The study showed a significant prolongation of progression-free survival with vandetanib versus placebo (hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.31-0.69; P <.001). The median duration of treatment in the randomized phase was 90.1 weeks for vandetanib and 39.9 weeks for placebo. The ZETA trial included many patients with indolent disease, as is evidenced by the median progression-free survival of 19.3 months in the placebo group (with an estimated progression-free survival of 30 months in the vandetanib group). Adverse events such as diarrhea, rash, nausea, and hypertension occurred in more than 30% of patients receiving vandetanib. A total of 19 (8%) patients developed protocol-defined QTc prolongation, but there were no reports of torsades de pointes.[39]

Cabozantinib. In 2012, the FDA approved the second TKI, cabozantinib, for the same indication as vandetanib, on the basis of the EXAM (Efficacy of XL184 in Advanced Medullary Thyroid Cancer) trial.[40] This drug is a TKI that targets 3 potentially important pathways in medullary thyroid cancer: *MET*, VEGF receptor 2, and *RET*.[41] The study showed the prolongation of progression-free survival to 11.2 months for cabozantinib versus 4 months for placebo (HR, 0.28; 95% CI, 0.19-0.4; P <.001). Cabozantinib had significant grade 3 or 4 side effects, including diarrhea, hand-foot syndrome, fatigue, and hypertension. In the study, 79% of the patients had dose reductions, of which 16% of patients discontinued their treatment. Grade 5 lethal toxicities occurred in 7% of patients, which included fistula, respiratory failure, sudden death, hemorrhage, and sepsis.[41]

Vandetanib and cabozantinib have shown significant prolongation of progression-free survival, and calcitonin and carcinoembryonic antigen levels decrease dramatically with these agents; however, no overall survival benefit was seen in these studies so far. These drugs need to be individualized to the patients because of their various side effects; thus, a great deal of clinical judgment is required before treating patients with them.

Sorafenib. In 2013, sorafenib, which is a multikinase inhibitor of *RET*, wild-type and *BRAF* V600E mutation, VEGF receptors 2 and 3, among others, was the third drug to be approved by the FDA for the treatment of ^{131}I-refractory, locally recurrent or metastatic, progressive, differentiated thyroid cancer.

The landmark DECISION study, which led to the FDA's approval of sorafenib, was a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial that included patients with locally recurrent or metastatic, progressive differentiated thyroid cancer.[42] The major efficacy outcomes measured included progression-free survival, overall survival, tumor response rate, and duration of response. The DECISION study demonstrated a significant prolongation in median progression-free survival of 10.8 months with sorafenib versus 5.8 months with placebo (HR, 0.59; 95% CI, 0.45-0.76; P <.001).[42]

Adverse events occurred in 204 (98.6%) of 207 patients receiving sorafenib during the double-blind period and in 183 (87.6%) of 209 patients receiving placebo. Most adverse events were grade 1 or 2, with the most frequent treatment-emergent adverse events in the sorafenib group being hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), and rash or desquamation (50.2%).[42] Sorafenib can prolong the QT/corrected QT (QTc) interval and can increase the risk for ventricular arrhythmias.[43] Also, sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous-cell lung cancer.[43,44]

External Beam Radiation Therapy

External beam radiation therapy is only used for palliative treatment of patients with advanced or inoperable thyroid cancer.[5] It is usually considered in patients aged >45 years who have grossly visible extrathyroidal extension and a high likelihood of residual disease during surgery.[5] It is also reserved for tumors that are unresponsive to therapy with ^{131}I.[5]

Posttreatment Management

TSH suppression therapy is recommended after surgery and after ^{131}I therapy, because differentiated thyroid cancers express TSH receptors that respond to TSH stimulation.[5] The cells respond by increasing sodium iodide symporters and thus increasing cell growth. TSH suppression can be achieved by using supraphysiologic doses of levothyroxine to suppress the TSH to <0.1 mU/L or up to 0.5 mU/L for lower-risk patients.[5] Serum thyroglobulin should be measured every 6 to 12 months in the same laboratory along with antithyroglobulin antibodies, because 25% of patients with thyroid cancer will produce this antibody, which falsely lowers the level of serum thyroglobulin.[5] Periodic neck ultrasound should also be performed in patients with partial thyroidectomy and in patients with total thyroidectomy who have not had ^{131}I ablation to monitor for tissue growth.[5]

Approximately 12 months after ablation, a single rhTSH-stimulated serum thyroglobulin measuring <0.5 ng/mL without antithyroglobulin antibody can identify patients who are completely free of tumor.[5] A disease-free status is achieved when there is no clinical evidence of tumor, no imaging evidence of tumor (negative whole-body scan), and undetectable serum thyroglobulin level with TSH stimulation in the absence of antibodies.[5] Such patients can then be followed up with annual thyroglobulin levels and thyroid hormone replacement.[5]

If the patient had high-risk disease, TSH should be suppressed to 0.1 to 0.5 mU/L for 5 to 10 years, and patients who had low-risk disease or who have become disease free should maintain a TSH of 0.3 to 2.0 mU/L.[5] If a patient is thyroglobulin positive (>10 ng/mL) and the ^{131}I whole-body scan is negative, a PET scan should be ordered to rule out any metastatic disease that would require further workup.[5] In patients with persistent disease, TSH should be maintained to <0.1 mU/L indefinitely.[5]

Conclusion

Thyroid cancer represents 3.8% of all new cases of cancer in the United States.[2] The prognosis and treatment of thyroid cancer depend on the type of cancer and the tumor stage at the time of diagnosis. Many thyroid cancers remain stable, microscopic, and indolent. Total thyroidectomy increases survival rates and decreases recurrence rates in patients with thyroid cancer. Treatment with ^{131}I has been an integral adjuvant role in the treatment of thyroid cancer. Molecular-targeted therapies, such as TKIs, have been approved in the past few years for the treatment of patients with advanced thyroid cancer. All of these treatment options have kept the mortality rate for thyroid cancer low, despite the recent increase in its incidence. ■

Author Disclosure Statement

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Stakeholder Perspective next page

STAKEHOLDER PERSPECTIVE

Predictive Models and Technology Present Opportunities to Support Early Diagnosis, Treatment, and Adherence to Guidelines

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PATIENTS: Differentiated thyroid cancer, which includes papillary and follicular cancers, represents approximately 90% of all cases of thyroid cancer. In their article in this issue of *American Health & Drug Benefits*, Nguyen and colleagues report the lifetime risk for thyroid cancer as 1.1% and the 5-year survival rate having risen to 97.8%, which is driven by early diagnosis in almost 70% of patients with localized cancer.[1] However, the incidence of thyroid cancer is rising by an average of 5.5% annually.[2] Rahib and colleagues project that breast, prostate, and lung cancers will remain the top cancers diagnosed by 2030.[2] They also predict that thyroid cancer will replace colorectal cancer as the fourth leading cancer diagnosed by 2030, and that melanoma and uterine cancers will become the fifth and sixth most common cancers, respectively.[2]

PAYERS: There is concern that the success achieved to date in overall survival in the face of increasing pressures to control costs has resulted in overly conservative treatment strategies.[3]

To promote high-quality care for patients with differentiated thyroid cancer, payers should focus on ways to support clinicians' adherence to the revised American Thyroid Association's management guidelines for patients with thyroid nodules and differentiated thyroid cancer.[4] Payers should also leverage their access to patient-level data and electronic medical records to develop predictive models that can assist in identifying patients at high risk for thyroid cancer, and provider adherence to treatment guidelines that are focused on early detection and treatment. This will help all stakeholders to maintain the treatment success rates that have been achieved in the past as incidence rates rise with an increasingly aging population.

The Medicare population should be of particular relevance to payers; because of their increasing age, Medicare beneficiaries may be at increased risk for thyroid cancer.[3] The elderly often present with more aggressive forms of cancer, including metastatic disease, larger tumors, and more extensive local growth.[3]

Boltz and colleagues conducted a study on the costs attributed to patients with differentiated thyroid cancer in the Medicare population using the Surveillance, Epidemiology, and End Results database to establish costs associated with disease stage and treatment options over 5 years.[3] The cumulative costs amounted to $17,669 per patient in the first year of treatment and $49,989 per patient by 5 years of treatment. Patients who had regional disease had higher costs at 1 year ($9578) and by 5 years ($8902) of treatment. Patients with distant disease had 1-year costs of $28,447 and 5-year costs of $20,103. Patients undergoing surgery and radiation had a $722 decrease in cost by 5 years of treatment. Boltz and colleagues conclude that differentiated thyroid cancer in the elderly is associated with significant economic burden that is largely attributable to patient demographics, stage of disease, and treatment modalities.[3]

The standard treatment approach to differentiated thyroid cancer involves multimodal treatment according to the American Thyroid Association management guidelines, yet their economic analysis showed that 55% of patients did not receive radioiodine therapy and 6.5% had additional types of radiation therapy, indicating they had received less aggressive care that is not consistent with current guidelines.[3]

Unlike the majority of patients with thyroid cancer who have excellent survival rates, patients who have high-risk factors have been identified as having the worst prognosis. Yang and colleagues reported on the development of a nomogram that is designed to help clinicians identify patients at high risk for death from thyroid cancer, which can be used by clinicians to design individualized treatment but can also potentially be used by managed care organizations with predictive modeling capability, where it could be applied across large populations.[5]

Yildirim conducted a study to determine prognostic factors that could be used to develop a mathematical model for predicting outcomes in patients with differentiated thyroid cancer.[6] He determined that age, tumor size, angioinvasion, and distant metastasis were significant predictors of outcomes that allowed for patients to be segmented into very low-risk, low-risk, high-risk, and very high-risk groups using logistic regression. The results of this study could serve as a foundation for a larger-

STAKEHOLDER PERSPECTIVE *Continued*

scale application of predictive models by managed care analytics departments.[6]

Health plans face significant challenges in population health management balancing the needs of their clients, while trying to engage their plan members and support the clinicians who deliver and manage their members' care. Managing the costs and quality of a population has resulted in the development of large, sophisticated databases that provide the potential for harnessing technology to predict which members are at risk and to directly communicate to members and physicians about at-risk patients so that early and aggressive treatment aligned with evidence-based guidelines can be initiated.

Thyroid cancer is a common malignancy of the endocrine system, in which early diagnosis and effective treatment can dramatically result in improved outcomes and reduced mortality. Leveraging existing technology, predictive models, electronic medical records, and communication across cross-functional healthcare stakeholders is a promising strategic approach to improve early diagnosis and treatment. ■

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